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(57) Abstract

The present invention provides a method and composition of medications used to treat inflammatory bowel disease. The invention further provides combinations of anti–atypical mycobacterial agents effective against the atypical mycobacterial strains. It also provides a method of potentiating the anti–atypical mycobacterial agents in treatment of inflammatory bowel disease by immunising patients with extracts of non–pathogenic mycobacteria.

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METHODS AND COMPOSITIONS FOR TREATING INFLAMMATORY BOWEL DISEASE

Technical Field

The invention relates to compositions and methods for the treatment of inflammatory bowel disease, such as Crohn's disease.

Background of the Invention

Inflammatory bowel disease (IBD) is a disorder of unknown aetiology characterised typically by diarrhoea, cramping, abdominal pains, weight loss and rectal bleeding. It encompasses such disorders as Crohn's disease, ulcerative colitis, indeterminate colitis, microscopic colitis and collagenous colitis. Its cause is unknown. However, in the past there has been some evidence that *Mycobacterium paratuberculosis* (Mp) and perhaps its various sub-strains, may play an infective role by entering the cells which make up the bowel wall. The source of this bacterium is unclear but may reside in other animals such as sheep, cattle, rabbits, as well as other humans. It may be transmitted to people perhaps via milk, contaminated water supplies, poorly cooked meat, etc. Although there has been long-standing controversy about the involvement of Mp in causation of Crohn's disease, recent applications of PCR usage are beginning to confirm that most Crohn's cases are indeed infected with this organism which is likely to be the causal infective agent. In the past, therapy directed at the eradication of Mp by using combined anti-TB drugs eg INH, pyrazinamide, streptomycin, ethambutol, rifampicin and PAS have been generally of little help to patients. In other words, although transient improvements in a proportion of patients did occur, no patient was cured. In fact, even if Mp had been the cause of this disease there was no effective therapy available for Mp since it was an "atypical mycobacterium" and for atypical mycobacteria there was no known therapy. Furthermore, since *Mycobacterium paratuberculosis* has a long division time multiple antimicrobial drugs are required to the treat the infection which has to be carried out for a long period of time - akin to the treatment used in the therapy of *Mycobacterium tuberculosis*. Furthermore, *Mycobacterium tuberculosis* therapy with the current drugs results in resistant strains forming. Such resistant strains do not become eradicated with known antimicrobial agents. Hence, there is no known effective cure for resistant TB.

Accordingly, there is a need for an effective treatment of inflammatory bowel disease, and in particular Crohn's disease. It is an object of this invention to provide such a treatment.

Surprisingly, the present inventor has discovered that the metabolism of the mycobacteria believed to be responsible for the symptoms of inflammatory bowel disorders may be inhibited long enough to cure the infection and thus relieve the symptoms, by administering to the patient a combination of anti-atypical mycobacterial agents and/or an immunising amount of a mycobacterial product.

Summary of the Invention

The present invention provides a method and composition of medications used to treat inflammatory bowel disease including Crohn's disease and colitis. The methods of the invention result in a cure of the infection and reversal of the clinical condition. The invention further provides combinations of anti-atypical mycobacterial agents effective against the atypical mycobacterial strains. It also provides a method of potentiating the anti-atypical mycobacterial agents in treatment of inflammatory bowel disease by immunising patients with extracts of non-pathogenic mycobacteria.

Thus, in a first embodiment, the invention provides a composition for the treatment of inflammatory bowel disease including three or more anti-atypical mycobacterial agents.

In a second embodiment, the invention provides a method for the treatment of inflammatory bowel disease including administering to a patient in need of said treatment an effective amount of at least three anti-atypical mycobacterial agents.

In a third embodiment, the invention provides a method for the treatment of inflammatory bowel disease including administering to a patient in need of said treatment an effective amount of at least three anti-atypical mycobacterial agents and immunising the patient with an immunising amount of a mycobacterial extract or product.

In a fourth embodiment, the invention provides a method for the treatment of inflammatory bowel disease including administering to a patient in need of said treatment an immunising amount of a mycobacterial extract or product.

In further embodiments, the invention provides (a) the use of a composition comprising three or more anti-atypical mycobacterial agents for the manufacture of a medicament for the treatment of inflammatory bowel disease; (b) the use of a composition including at least three anti-atypical mycobacterial agents and a mycobacterial extract or product for the manufacture of a medicament for the treatment of inflammatory bowel disease; and (c) the use of a mycobacterial extract or product for the manufacture of a medicament for the treatment of inflammatory bowel disease.

Description of the Invention

This invention discloses a method of use and compositions useful in the treatment of Crohn's disease and colitis and of other inflammatory bowel diseases using various combinations of anti-atypical mycobacterial drugs.

In the composition of the first embodiment of the invention, or the methods of the second or third embodiments, valid combinations of anti-atypical mycobacterial agents include triple (three drugs) groupings of anti-atypical mycobacterial agents, or indeed larger combinations for exceptional situations, eg where resistant strains emerge. Four, five and even six drug combinations may be required in patients with resistant *Mycobacterium paratuberculosis* strains. Suitable anti-atypical mycobacterial agents include, but are not limited to, clarithromycin, rifabutin, rifampicin, azithromycin,

roxithromycin, amikacin, clofazimine, ethambutol, ofloxacin, ciprofloxacin and oxazolidinone. These may be co-used with one or more 5-aminosalicylic acid compounds or 4-aminosalicylic acid compounds such as mesalazine, olsalazine, salazopyrin or para-amino salicylic acid. Typically, at least one of the anti-atypical mycobacterial agents is rifabutin or clarithromycin. More typically, the composition of the first embodiment includes rifabutin, clarithromycin and clofazimine. Similarly, the methods of the second and third embodiments usually involve the administration to the patient of an effective amount of a combination of rifabutin, clarithromycin, and clofazimine.

Surprisingly, the combination of three or more anti-atypical mycobacterial agents exhibits a substantially greater effect against inflammatory bowel disease than would have been expected from each anti-atypical mycobacterial agent alone.

Typically, the composition of the present invention may include between 10-500mg of each of three or more anti-atypical mycobacterial agents. More typically, the composition of the present invention may include between 10-250mg of each of three or more anti-atypical mycobacterial agents. Even more typically, the composition of the present invention may include rifabutin present at between 50-250mg, more typically, approximately 150mg, clarithromycin at between 200-300mg, more typically, approximately 250mg, and clofazimine at between 10-150mg, more typically, approximately 50mg. Further, other anti-atypical mycobacterial agents may be present in amounts in accordance with known dosages.

Typically, the composition of the present invention may be available in the form of a tablet containing each of three or more anti-atypical mycobacterial agents present in a compressed powdered form. Alternatively, the composition of the present invention may be available in the form of a tablet/capsule containing one or more of the anti-atypical mycobacterial agents in a microencapsulated form. As another possibility, the composition of the present invention may be available in the form of a tablet/capsule containing one of the three or more anti-atypical mycobacterial agents present in a powdered form, and the remaining anti-atypical mycobacterial agents present in a microencapsulated form. As a further possibility, the composition of the present invention may be available in the form of a tablet/capsule containing each of three or more anti-atypical mycobacterial agents present in a microgranulated form. In even further possibilities, the composition of the present invention may be available in the form of a tablet(s) containing one or more of the anti-atypical mycobacterial agents within a capsule, a capsule(s) containing one or more of the anti-atypical mycobacterial agents within a tablet, a capsule(s) containing one or more of the anti-atypical mycobacterial agents within an outer capsule containing the other anti-atypical mycobacterial agents, or any combination of the above.

In a preferred form, the composition of the invention consists of an inner capsule containing rifabutin, within an outer capsule containing clarithromycin and clofazimine,

wherein clarithromycin and clofazimine may be present in powdered, microencapsulated, or microgranulated forms.

Typically, the methods of the present invention may be carried out by administration of one or more tablets/capsules containing each of three or more anti-atypical mycobacterial agents as described in the immediately preceding paragraph, or through the administration of each of three or more anti-atypical mycobacterial agents separately.

In the method of the fourth embodiment a patient previously not treated or on current anti-inflammatory therapies is treated by immunisation with a mycobacterial extract or product (living or dead, or its extracted wall and DNA components) as an immunising agent to stimulate leucocytes in the immunised patient. Such immunising agents may be extracts or products from known, non-pathogenic mycobacteria such as *M. vaccae* or *M. phlei*. As used herein, the expression "mycobacterial extract or product" means whole killed mycobacteria or mycobacterial extract, with or without adjuvants. An example of a suitable mycobacterial product or extract is Regressin, available from Bioniche of London, Ontario, Canada.

The mycobacterial product may be used to recurrently immunise the patient using the product as an immunostimulant. The mycobacterial product can be administered via any of several routes, such as oral, intravenous, intramuscular or subcutaneous. Such immunisations can rid the patient of the Mp infection and have the ability to cure the disease or place the patient into a prolonged remission. Administration of the mycobacterial product or extract is typically from weekly to monthly, but may be more or less frequent. An appropriate treatment regime may be arrived at readily by a medical practitioner in any particular case, given the teaching herein.

A preferred therapy with *Mycobacterium phlei* extract (eg Regressin) includes a weekly immunisation program, increasing the dosage by 50μg of the extract every week until the patient develops fever, rigors and nausea. The dose is then dropped by 50μg to the lower level and the patient continues maintenance immunisation on a monthly basis. The treatment can last from 6 weeks up to a monthly immunisation program of 2 years or more.

In another form of therapy standard anti-inflammatory therapy can be combined with recurrent Regressin immunisation.

In the method of the third embodiment, at least three anti-atypical mycobacterial agents are combined with use of a mycobacterial extract or product as an immunising agent. The mycobacterial extract or product for use in the method of the third embodiment may be a mycobacterial extract or product as described above with reference to the third embodiment. For example, rifabutin may be combined with clarithromycin and clofazimine in the therapy and further combined with an immunising protocol using *M. phlei* extract (e.g. Regressin).

In the methods of the invention, the anti-atypical mycobacterial agents are usually used continuously over a period of 3 to 36 months. Dosages of the anti-atypical mycobacterial agents are generally in accordance with known dosage ranges. For example, the typical dosage of clarithromycin is from 250mg to 1.5g per day, more typically about 750mg per day; the typical dosage of rifabutin is from 150mg to 750mg per day, more typically about 450mg per day; the typical dosage of clofazimine is from about 1mg/kg to about 6mg/kg, more typically about 2mg/kg; the typical dosage of ethambutol is up to about 15mg/kg; and the typical dosage of azithromycin is from 250mg to 1000mg per day, more typically about 500mg per day.

The inflammatory process may be monitored by colonoscopy and biopsy, as well as various blood parameters, during the course of treatment in accordance with the invention.

Preferably, the method of the third embodiment consists of a 24 month treatment daily of clarithromycin combined with rifabutin and clofazimine, at dosages as described above. In a more preferred method, the patient will also be recurrently immunised at intervals using a mycobacterial extract of *M. phlei* (Regressin). This can be given orally, intravenously, subcutaneously, or in combinations of the above. Doses of the mycobacterial extract can be given in any frequency ranging from 25μg to 500μg, more typically, 50μg to 500μg. However, weekly to monthly, typically weekly or monthly, is usually adequate to maintain immuno-stimulation.

The methods of the present invention can also be combined with one or more milder anti-TB agents such as salazopyrin, olsalazine or mesalazine, as well as other less known aminosalicylic acids. The 4-aminosalicyclic acids or 5-aminosalicylic acids can be combined with any three or more of the anti-atypical mycobacterial agents mentioned above. Dosages of these agents are generally known. For example the typical dosage range for salazopyrin is in the range of from about 500mg to 4g per day; and for olsalazine or mesalazine from about 500mg to about 3g per day. Thus, the composition of the first embodiment may further include an agent effective against tuberculosis. Similarly, the method of the second or third embodiments may further include administering an effective amount of an agent effective against tuberculosis.

Compositions for administration of the invention may be prepared by means known in the art for the preparation of compositions (such as in the art of pharmaceutical compositions) including blending, grinding, homogenising, suspending, dissolving, emulsifying, dispersing and where appropriate, mixing of the anti-atypical mycobacterial agent together with selected excipients, diluents, carriers and adjuvants.

For oral administration, the pharmaceutical composition may be in the form of tablets, lozenges, pills, troches, capsules, elixirs, powders, including lyophilised powders, solutions, granules, suspensions, emulsions, syrups and tinctures. Slow-release, or delayed-release, forms may also be prepared, for example in the form of coated particles, multi-layer tablets or microgranules.

Solid forms for oral administration may contain pharmaceutically acceptable binders, sweeteners, disintegrating agents, diluents, flavourings, coating agents, preservatives, lubricants and/or time delay agents. Suitable binders include gum acacia, gelatin, corn starch, gum tragacanth, sodium alginate, carboxymethylcellulose or polyethylene glycol. Suitable sweeteners include sucrose, lactose, glucose, aspartame or saccharine. Suitable disintegrating agents include corn starch, methylcellulose, polyvinylpyrrolidone, xanthan gum, bentonite, alginic acid or agar. Suitable diluents include lactose, sorbitol, mannitol, dextrose, kaolin, cellulose, calcium carbonate, calcium silicate or dicalcium phosphate. Suitable flavouring agents include peppermint oil, oil of wintergreen, cherry, orange or raspberry flavouring. Suitable coating agents include polymers or copolymers of acrylic acid and/or methacrylic acid and/or their esters, waxes, fatty alcohols, zein, shellac or gluten. Suitable preservatives include sodium benzoate, vitamin E, alpha-tocopherol, ascorbic acid, methyl paraben, propyl paraben or sodium bisulphite. Suitable lubricants include magnesium stearate, stearic acid, sodium oleate, sodium chloride or talc. Suitable time delay agents include glyceryl monostearate or glyceryl distearate.

Liquid forms for oral administration may contain, in addition to the above agents, a liquid carrier. Suitable liquid carriers include water, oils such as olive oil, peanut oil, sesame oil, sunflower oil, safflower oil, arachis oil, coconut oil, liquid paraffin, ethylene glycol, propylene glycol, polyethylene glycol, ethanol, propanol, isopropanol, glycerol, fatty alcohols, triglycerides or mixtures thereof.

Suspensions for oral administration may further include dispersing agents and/or suspending agents. Suitable suspending agents include sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, poly-vinyl-pyrrolidone, sodium alginate or cetyl alcohol. Suitable dispersing agents include lecithin, polyoxyethylene esters of fatty acids such as stearic acid, polyoxyethylene sorbitol mono- or di-oleate, -stearate or -laurate, polyoxyethylene sorbitan mono- or di-oleate, -stearate or -laurate and the like.

The emulsions for oral administration may further include one or more emulsifying agents. Suitable emulsifying agents include dispersing agents as exemplified above or natural gums such as gum acacia or gum tragacanth.

Examples

Example 1: Treatment of patients with inflammatory bowel disease using a combination of anti-atypical mycobacterial agents

Fifteen patients, aged 13 to 58, were treated with various protocols of anti-mycobacterial agents. Twelve patients had Crohn's disease and three ulcerative colitis. Presence of *Mycobacterium paratuberculosis* was identified in nine of these patients. A combination of clarithromycin (250mg to 1.5 grams per day), rifabutin (150mg to 750mg per day) and clofazimine (3mg/kg to 10mg/kg) was used. Rapid clinical remission was

obtained in these patients with cessation of prednisone, azathioprine, and 5ASA compounds and settlement clinically of their inflammatory bowel disease.

After four months of treatment, five patients were examined colonoscopically. Two of these patients had normalised the colonic and terminal ileum mucosa while three continued to have patchy inflammatory changes and histological presence of minimal inflammatory infiltrate with some eosinophils.

In these three patients, a combination of clarithromycin and rifabutin (same dosages as above) together with added clofazimine, 2mg per kg, made up a preferred therapy. Seventy percent of the patients improved dramatically at 8 months with removal of all need for anti-inflammatory bowel disease medications. No prednisone, azathioprine or 5ASA compounds were used. The inflammatory process in these patients was no longer detectable and even histologically no evidence of IBD was present when viewed under the microscope. However, in one patient who was sensitive to rifabutin (marked headaches and fever) the rifabutin was changed to ethambutol at a dose of 400mg twice daily. This dose was increased at one stage to 50mg per kg in an attempt to reverse the inflammatory process and then reduced to 10mg per kg. The patient also obtained reversal of the inflammatory process with loss of diarrhoea, loss of bleeding, and ultimately loss of urgency. In yet a further patient four drugs were used simultaneously because of resistance to clarithromycin. Azithromycin, 500mg each morning (range 250 - 1,500mg) was used in combination with rifabutin, clofazimine, and ethambutol.

Example 2: Treatment of patient with inflammatory bowel disease using a microbial extract

A 34 year old patient with two bowel resections and a stricturotomy while on standard Crohn's disease therapy consisting of azopiathrin, prednisone and mesalazine received an immuno-stimulatory injection of Regressin. This was given intra-muscularly and later orally in a starting dose of 500μg, followed by 500μg weekly for four weeks, and then monthly.

Two years after recurrent oral immunisation on a weekly and then monthly basis, the patient remains symptom-free and off all therapy, suggestive of Crohn's disease reversal and disappearance. At colonoscopy the anastomosis site was free of Crohn's disease.

Example 3: Treatment of Severe Crohn's Disease using Rifabutin- Macrolide-Clofazimine Combination

Patients failing maximal conventional therapy were commenced prospectively on a combination of rifabutin (450mg/day), clarithromycin (750mg/day), and clofazimine (2mg/kg). Azathiaprine was terminated while 5-ASA and steroids were tapered then ceased. Progress was monitored by colonoscopy, cross-sectional ultrasound, haematology values and the Harvey-Bradshaw activity index. After 8-12 months, 10 patients achieved near-complete control of Crohn's disease on the combination therapy alone. Ileal strictures dilated to normal ultrasound wall thickness in all of the five patients examined.

Extensive pseudopolyp crops regressed from the colon in the patient suffering from this condition, defunctioning ileostomy was closed at 11 months in the patient suffering from this condition, reversal from inflamed to histologically uninflamed ileal and colonic mucosa was observed in five of twelve patients suffering from this condition. All patients had essentially normalised haematologic values after 8-12 months of treatment. In 2 patients, Crohn's disease progressed 2-3 months after cessation of steroids which were subsequently reintroduced while continuing the combined therapy of the present invention. The Harvey-Bradshaw index fell from 15.5 to 2.5.

Example 4: Composition for oral administration to patient with inflammatory bowel disease

A composition was prepared containing 150mg Rifabutin, 250mg Clarithromycin and 50mg Clofazimine. The composition was presented in the form of a capsule containing each of the anti-atypical mycobacterial agents in a microencapsulated form.

Example 5: Composition for oral administration to patient with inflammatory bowel disease

A composition was prepared containing 150mg Rifabutin, 250mg Clarithromycin and 50mg Clofazimine. The composition was presented in the form of an inner capsule containing rifabutin, within an outer capsule containing clarithromycin and clofazimine, wherein clarithromycin and clofazimine are present in powdered form.

Example 6: Composition for oral administration to patient with inflammatory bowel disease

A composition was prepared containing 150mg Rifabutin, 250mg Clarithromycin and 50mg Clofazimine. The composition was presented in the form of an inner capsule containing rifabutin, within an outer capsule containing clarithromycin and clofazimine, wherein clarithromycin and clofazimine are present in microencapsulated form.

Example 7: Composition for oral administration to patient with inflammatory bowel disease

A composition was prepared containing 150mg Rifabutin, 250mg Clarithromycin and 50mg Clofazimine. The composition was presented in the form of an inner capsule containing rifabutin, within an outer capsule containing clarithromycin and clofazimine, wherein clarithromycin and clofazimine are present in microgranulated form.

Industrial Applicability

The present invention provides a method and composition of medications used to treat inflammatory bowel disease. The invention further provides combinations of anti-atypical mycobacterial agents effective against the atypical mycobacterial strains. It also provides a method of potentiating the anti-atypical mycobacterial agents in treatment of inflammatory bowel disease by immunising patients with extracts of non-pathogenic mycobacteria.

CLAIMS

1. A composition for the treatment of inflammatory bowel disease including three or more anti-atypical mycobacterial agents.

2. The composition of claim 1, wherein said anti-atypical mycobacterial agents are selected from the group consisting of: clarithromycin, rifabutin, rifampicin, azithromycin, roxithromycin, amikacin, clofazimine, ethambutol, ofloxacin, ciprofloxacin and oxazolidinone.

3. The composition of claim 1, including rifabutin and clarithromycin.

4. The composition of claim 1, including rifabutin, clarithromycin and clofazimine.

5. The composition of claim 1, further including at least one 5-aminosalicylic acid compound or 4-aminosalicylic acid compound.

6. The composition of claim 5, wherein said 5-aminosalicylic acid compound or 4-aminosalicylic acid compound is selected from the group consisting of: mesalazine, olsalazine, salazopyrin and para-amino salicylic acid.

7. A method for the treatment of inflammatory bowel disease including administering to a patient in need of said treatment an effective amount of at least three anti-atypical mycobacterial agents.

8. A method for the treatment of inflammatory bowel disease including administering to a patient in need of said treatment an effective amount of at least three anti-atypical mycobacterial agents and immunising the patient with an immunising amount of a mycobacterial extract or product.

9. The method of claim 7 or 8, wherein said anti-atypical mycobacterial agents are selected from the group consisting of: clarithromycin, rifabutin, rifampicin, azithromycin, roxithromycin, amikacin, clofazimine, ethambutol, ofloxacin, ciprofloxacin and oxazolidinone.

10. The method of claim 7 or 8, including administering to said patient rifabutin and clarithromycin.

11. The method of claim 7 or 8, including administering to said patient rifabutin, clarithromycin and clofazimine.

12. The method of claim 7 or 8, including administering to said patient at least one 5-aminosalicylic acid compound or 4-aminosalicylic acid compound.

13. The method of claim 12, wherein said 5-aminosalicylic acid compound or 4-aminosalicylic acid compound is selected from the group consisting of: mesalazine, olsalazine, salazopyrin and para-amino salicylic acid.

14. A method for the treatment of inflammatory bowel disease including administering to a patient in need of said treatment an effective amount of a mycobacterial extract or product.

15. The method of claim 8 or 14, wherein said mycobacterial extract or product includes an extract or product from non-pathogenic mycobacteria.

16. The method of claim 15, wherein said non-pathogenic bacteria include *M. vaccae* or *M. phlei*.

17. The method of claim 8 or 14, wherein said amount of a mycobacterial extract or product ranges from between about 25μg to about 500μg.

18. The method of claim 8 or 14, wherein said mycobacterial extract or product is administered orally, intravenously, intramuscularly, subcutaneously, or any combination thereof.

19. The method of claim 8 or 14, wherein said immunising amount of a mycobacterial extract or product is administered from weekly to monthly.

20. The method of claim 8 or 14, wherein said immunising amount of a mycobacterial extract or product is administered weekly.

21. The method of claim 8 or 14, wherein said mycobacterial extract or product is Regressin.

22. Use of a composition including three or more anti-atypical mycobacterial agents for the manufacture of a medicament for the treatment of inflammatory bowel disease.

23. Use of a composition including at least three anti-atypical mycobacterial agents and a mycobacterial extract or product for the manufacture of a medicament for the treatment of inflammatory bowel disease.

24. Use of a composition according to claim 22 or 23, wherein said anti-atypical mycobacterial agents are selected from the group consisting of: clarithromycin, rifabutin, rifampicin, azithromycin, roxithromycin, amikacin, clofazimine, ethambutol, ofloxacin, ciprofloxacin and oxazolidinone.

25. Use of a composition according to claim 22 or 23, including rifabutin and clarithromycin.

26. Use of a composition according to claim 22 or 23, including rifabutin, clarithromycin and clofazimine.

27. Use of a composition according to claim 22 or 23, further including at least one 5- aminosalicylic acid compound or 4-aminosalicylic acid compound.

28. Use of a composition according to claim 22 or 23, wherein said 5-aminosalicylic acid compound or 4-aminosalicylic acid compound is selected from the group consisting of: mesalazine, olsalazine, salazopyrin and para-amino salicylic acid.

29. Use of a mycobacterial extract or product for the manufacture of a medicament for the treatment of inflammatory bowel disease.

30. Use according to claim 23 or 29, wherein said mycobacterial extract or product includes an extract or product from non-pathogenic mycobacteria.

31. Use according to claim 30, wherein said non-pathogenic bacteria include *M. vaccae* or *M. phlei*.

32. Use according to claim 23 or 29, wherein said mycobacterial extract or product is used in an amount from between about 25μg to about 500μg.

33. Use according to claim 23 or 29, wherein said mycobacterial extract or product is Regressin.

INTERNATIONAL SEARCH REPOR.

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A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Derwent WPAT; CHEM AB; MEDLINE, MYCOBACT, INFLAMMATORY BOWEL; CROHN'S, COLITIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Shafran, S D, Singer, J, Zarowny, D P, Phillips, P, Salit, I, Walmsley, S L, Fong, I W, Gill, M J, Rachlis, A R, Lalonde, R C, Fanning, N M, Tsoukas, C M, A Comparison of two regimens for the treatment of Mycobacterium avium complex bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. Canadian HIV Trials Network Protocol 010 Study Group, New England Journal of Medicine, Volume 335(6); 377-383, August 1996.	22, 24, 25
X	Yajko, D M et al, In vitro activities of rifabutin, azithromycin, ciprofloxacin, clarithromycin, clofazimine, ethambutol, and amikacin in combinations of two, three and four drugs against Mycobacterium avium. Antimicrobial Agents Chemotherapy, Volume 40(3); 743-749, March, 1996.	22, 24, 25

[X] Further documents are listed in the continuation of Box C

[ ] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 July 1998	24 JUL 1998
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929	Authorized officer A WILCOX Telephone No.: (02) 6283 2243

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 98/00222

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Rastogi, N et al, Activity of clarithromycin compared with those of other drugs against Mycobacterium paratuberculosis and further enhancement of its extracellular and intracellular activities by ethambutol. Antimicrobial Agents Chemotherapy, Volume 36(12): 2843-2846: 1992.	1,2,3,7,9,22,24,25
X	Chiodini, R J. In vitro antimicrobiol susceptibility of a Mycobacterium sp. isolated from patients with Crohn's disease, Antimicrobial Agents Chemotherapy Volume 26(6): 930-932: 1984.	1,22
X	Pradhan, S N, Maickel, R P, Dutta, S N, Pharmacology In Medicine: Principles And Practice. SP Press International Inc. 1986, pages 847-858. At page 847, Column 2 last lines, a combination treatment of drugs is disclosed.	1,35,22, 27, 28
X	Berkow, R, Fletcher, A J and Beers, M H, The Merck Manual of Diagnosis And Therapy. Merck Research Laboratories, New Jersey 1992. Pages 138-146.	1,2,7-9,14,15,17-20,22-24,29,30,32
X	Goodman Gilman, A, Goodman, L S, Roll, T W, Murad, F, Goodman and Gilman's The Pharmacological Basis of Therapeutics, Macmillan Publishing Company. New York. 1985 1199-1212.	1,2,7,9,22,24
X	Bennett, J C and Plum, F Cecil Textbook of Medicine, 20th Edition, W B Saunders Company, Philadelphia 1996 Pages 1683-1691.	1-4,7-11,14-20, 22-26, 29-30, and 32